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REVIEW

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Expanding telmisartan's therapeutic horizon: exploring its multifaceted mechanisms beyond cardiovascular disorders

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Abstract

Background Telmisartan, a potent angiotensin II type-1 receptor blocker as well as partial PPAR–gamma agonist, has emerged as a versatile therapeutic agent with diverse pharmacological actions beyond its primary indication for essential hypertension. This review explores the complex mechanisms of action of telmisartan and clarifies its effectiveness in an inflammation, cancer, metabolic, and CNS disorders.

Main body Telmisartan inhibits many biochemical processes involved in the control of the cardiovascular system, such as vascular smooth muscle contraction, aldosterone production, and sympathetic tone modulation, by specifically targeting the angiotensin II type-1 receptor. Its distinct partial agonist action toward peroxisome proliferator-activated receptor gamma also imparts anti-inflammatory, antiproliferative, and antioxidant activities, making it a viable treatment for various diabetic patients who have atherosclerosis and myocardial infarction.

Conclusion Telmisartan's diverse pharmacological actions, encompassing anti-inflammatory, neuroprotective, nephroprotective, anticancer, and anti-anxiety properties, position it as a promising treatment option for a broad spectrum of medical conditions.

Keywords Telmisartan, Neuroinflammation, Diabetic retinopathy, Diabetic nephropathy, Endotoxin-induced uveitis, Crohn's disease

Background

Telmisartan, a nonpeptide antagonist directed at the angiotensin II type-1 (AT1) receptor, has surfaced as a versatile therapeutic option, demonstrating notable effectiveness and longevity in managing essential hypertension [1]. Its unique mode of action entails the targeted and enduring inhibition of the AT1 receptor's reactivity to angiotensin II, while preserving the functionality of other receptor systems implicated in cardiovascular control [2]. This selectivity not only forms the basis of its powerful antihypertensive action but also lays the groundwork for its diverse pharmacological characteristics [3].

In addition to its role as an angiotensin receptor blocker (ARB), telmisartan exhibits partial agonist activity toward the peroxisome proliferator-activated receptor gamma (PPAR-γ) [4]. This unique dual activity confers a myriad of additional benefits, including antioxidative, anti-inflammatory, and antiproliferative effects, particularly in conditions such as atherosclerosis [5]. Such pleiotropic effects position telmisartan as a promising therapeutic option for diabetic patients with myocardial infarction, offering a comprehensive approach to cardiovascular management beyond blood pressure control [6].

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Additionally, telmisartan's capacity to mitigate fibrotic alterations linked to diabetes-related cardiac fibrosis by activating endogenous PPARδ [4] and enhancing STAT3 [7, 8] expression highlights its potential in addressing diverse pathological pathways [9]. The activation of PPARδ not only maintains a balance in metabolism and inflammation [10] but also contributes to cardiac protection, thereby broadening telmisartan's therapeutic scope beyond hypertension [11].

Furthermore, telmisartan's influence extends beyond cardiovascular well-being, encompassing a range of advantageous effects on metabolic syndrome, neuroprotection [12], and nephroprotection. Its anti-inflammatory [13], antioxidative [14], antineoplastic [15], and nephroprotective [16] attributes further emphasize its potential as a valuable therapeutic agent across various diseases and disorders [17].

In this extensive review, we explore the multifaceted mechanisms of action of telmisartan, shedding light on its diverse pleiotropic effects and underscoring its potential as a fundamental component in the management of cardiovascular conditions and beyond. In this study, we examined over 323 research papers, with 199 of them being thoroughly included in our analysis. By meticulously analyzing the available literature, our objective is to offer valuable insights into the wide-ranging therapeutic capabilities of telmisartan, facilitating its exploration across diverse clinical scenarios.

Methodology

The scope of the review article on telmisartan will encompass its pharmacological properties, therapeutic indications, and emerging research trends for treatment of other than cardiovascular disorders. The objectives include evaluating the efficacy of telmisartan in the management of various CNS, cancer, diabetes, and its complications, exploring its potential mechanisms of action, and discussing its comparative effectiveness. For comprehensive coverage of literature on telmisartan, relevant databases such as PubMed, Web of Science, Scopus, and Google Scholar were utilized. A comprehensive search strategy was developed using keywords such as "telmisartan plus neurological disorders," "telmisartan + metabolic syndrome," "telmisartan and Diabetes," Cancer and telmisartan, etc., and search filters will be employed to refine the search and capture relevant literature on telmisartan's pharmacology. Search results were screened based on relevance to the review's objectives. Titles and abstracts were reviewed to assess their suitability for inclusion in the review. Studies focusing on telmisartan's pharmacological properties were prioritized for further evaluation. Inclusion criteria include studies published in English, observational studies, meta-analyses investigating telmisartan's efficacy for other than cardiovascular disorders in preclinical studies. Exclusion criteria comprise clinical trials, case reports, and studies with insufficient data or irrelevant outcomes. During the study, we examined over 323 research papers, with 199 of them being thoroughly included in our analysis. Full-text articles of potentially relevant studies were retrieved through institutional subscriptions, interlibrary access, or direct contact with authors. Selected studies were critically evaluated for their quality and validity. Factors including study design, sample size, methodology, and risk of bias were considered in the assessment.

Relevant data from selected studies were extracted using a standardized data extraction form. Key information including study characteristics, type of animal models, intervention details, outcomes, and conclusions was systematically recorded for creation of review. Findings from the selected studies were synthesized to address the review's research questions and objectives. Synthesized information was organized and presented in a tabular form for different disorders and diseases.

The review process involved continuous literation, with ongoing refinement of search strategies and inclusion/exclusion criteria to ensure comprehensive coverage of literature and alignment with the review's objectives. Additionally, updates were made to incorporate new findings and emerging research trends on telmisartan's therapeutic applications beyond cardiovascular disorders. (Methodology section was included to provide clarity and reproducibility).

Neuroinflammation and telmisartan

Angiotensin receptor II induces inflammation and oxidative stress via ROS production through the NADPH oxidase complex [18, 19]. Toll-like receptors (TLRs) and PPARγ receptors in the CNS play vital roles in neuroinflammation [20]. Excessive RAS activation, especially through AT1 receptors, contributes to brain inflammation [21, 22]. IL-1β, generated by microglia, has diverse roles and is implicated in neurodegenerative disorders [23, 24].

Telmisartan induces PPARγ activation independently of AT1R, preventing NFκB-mediated inflammatory cascades [13]. PPARγ activation leads to a dose-dependent increase in SARM expression, a negative regulator of pro-inflammatory cytokines [25].

Telmisartan reduces LPS-induced inflammation in neuronal cells via SARM activation through TLR4 signaling independently of AT1R [13]. TLR4 activation triggers NFκB, AP1, and IRF3, with a focus on MyD88-mediated pro-inflammatory cytokine mechanisms [26].

Telmisartan reduces IL-1β-induced COX-2 expression, PGE2 release, and ROS production. Telmisartan

mitigates IL-1β-induced upregulation of IL-1R1 receptor and NOX-4 mRNA expression [27]. Telmisartan attenuates hydrogen peroxide-induced COX-2 gene expression and reduces JNK and c-Jun activation. Telmisartan's neuroprotective effects are independent of PPARγ activation, as confirmed in primary rat cortical neurons [28, 29].

In conclusion, telmisartan demonstrates a multifaceted approach to neuroprotection by modulating specific pathways associated with inflammation and oxidative stress. These findings highlight its potential therapeutic role in neurodegenerative diseases.

Ocular inflammation and telmisartan

Endotoxin-induced uveitis (EIU) serves as an animal model for acute ocular inflammation induced by lipopolysaccharide (LPS) [30, 31]. Severe vision impairment complications include retinal vasculitis, retinal detachment, and glaucoma. Angiotensin II, a key renin-angiotensin system effector, interacts with AT_1 and AT_2 receptor [32, 33]. Recent studies reveal diverse biological roles of angiotensin II, including modulation of angiogenesis, vascular remodeling, and inflammation [34]. Angiotensin II enhances vascular permeability [35], induces chemokines and adhesion molecules, and influences inflammatory cell proliferation and differentiation. AT1R blockade, including telmisartan, effectively attenuates these inflammatory processes [36–38]. Upregulation of AT1R is associated with ocular inflammation in EIU [39]. Telmisartan effectively attenuates inflammatory parameters, including ICAM-1-mediated leukocyte adhesion and infiltration in EIU eyes. LPS stimulation leads to the upregulation of inflammatory mediators contributing to EIU development. ICAM-1 plays a pivotal role in leukocyte adhesion; its upregulation is inhibited by telmisartan. Telmisartan suppresses retinal ICAM-1 upregulation and mitigates various EIU-induced cytokines [40, 41]. The anti-inflammatory effects are associated with downregulation of NF-κB-induced molecules [42]. Insights into the RAS highlight its involvement in various inflammatory conditions, such as atherosclerosis, cerebral infarction, and pancreatitis [36]. Telmisartan substantially reduces anterior-chamber cell infiltration but shows limited impact on protein leakage [43].

Anti-inflammatory effects of telmisartan in Experimental Autoimmune Uveitis (EIU), a model for studying ocular inflammation. Telmisartan is noted for its ability to target important inflammatory mediators such as ICAM-1 (intercellular adhesion molecule-1), various cytokines, and molecules induced by NF-κB (nuclear factor-kappa B), a key transcription factor involved in inflammation. The reference to ICAM-1 suggests that telmisartan may inhibit the adhesion of immune cells to vascular endothelial cells, thereby reducing inflammation. Additionally, by modulating cytokines, which are signaling molecules involved in the immune response, telmisartan likely attenuates the inflammatory cascade in EIU. NF-κB-induced molecules further emphasize the drug's ability to interfere with transcriptional processes that promote inflammation.

Diabetes-induced vascular inflammation and telmisartan

Individuals with diabetes experience exposure of the endothelium to uncontrolled high glucose levels [44]. Endothelial dysfunction is the fundamental pathophysiology in diabetic macrovascular complications [45, 46]. Hyperglycemia triggers inflammatory responses crucial in the development of diabetic macrovascular diseases, including atherosclerotic coronary artery and cerebrovascular diseases [39]. Adhesion of inflammatory leukocytes to the vascular endothelium is a pivotal step in atherosclerosis development [47]. Adhesion molecules like VCAM-1, intercellular adhesion molecule-1, and endothelial-leukocyte adhesion molecule-1 play a role in leukocyte adhesion, leading to vascular inflammation [48]. Angiotensin II type-1 receptor blockers (ARBs), including telmisartan, are prescribed for hypertensive patients with diabetes mellitus [49]. Early reduction of inflammatory leukocyte homing and attachment to the endothelium is considered an effective therapeutic strategy. Telmisartan, an ARB, protects against vascular inflammation induced by hyperglycemia. Reports suggest that telmisartan reduces vascular inflammation by inhibiting the expression of IKKβ in endothelial cells [1]. Telmisartan induces GSK3β-Ser9 phosphorylation in endothelial cells. GSK3β-Ser9 phosphorylation decreases hyperglycemia-induced NFκB p65-Ser536 phosphorylation, VCAM-1 expression, and adhesion of THP-1 monocytes. GSK3β-S9A, a constitutively active mutant of GSK3β, restores the inhibition of NFκB p65-Ser536 phosphorylation, VCAM-1 expression, and THP-1 monocyte adhesion by telmisartan [1].

Telmisartan inhibits IKKβ expression in a GSK3β-Ser9 phosphorylation-dependent manner. Among various ARBs, only telmisartan demonstrates an increase in GSK3β-Ser9 phosphorylation. Telmisartan treatment mitigates HFD-induced upregulation of NFκB p65-Ser536 phosphorylation, VCAM-1 expression, and IKKβ expression in aortic tissues. Telmisartan alleviates hyperglycemia-exacerbated vascular inflammation by inducing GSK3β-Ser9 phosphorylation, inhibiting IKKβ expression, NFκB p65-Ser536 phosphorylation, and VCAM-1 expression in a PPARγ-independent manner. Telmisartan operates within diabetes by engaging with crucial signaling molecules implicated in inflammation and vascular irregularities, including GSK3β, IKKβ, NF-κB, and VCAM-1. Through its

influence on these pathways, telmisartan can alleviate the inflammatory reactions linked to diabetes and its accompanying complications, offering promising therapeutic possibilities for individuals with diabetes.

Chronic inflammation

The renin–angiotensin system produces angiotensin II, activating the AT1 receptor, leading to oxidative stress and inflammation [50]. Telmisartan, an AT1 receptor antagonist, also acts as a partial agonist on peroxisome proliferator-activated receptor-γ (PPAR-γ), providing antioxidative and anti-inflammatory effects [51]. Recent studies highlight telmisartan's additional PPAR-γ partial agonist activity, impacting metabolic and inflammatory pathways, improving left ventricular functions, and showing benefits in post-infarct ventricular remodeling [51, 52]. Telmisartan's dose–response relationship in animal models of chronic inflammation suggests antiproliferative and anti-arthritic activities, inhibiting inflammatory reactions [53]. Tissue injury triggers pro-inflammatory cytokine release, but telmisartan's PPAR-γ activation decreases hypertrophic prostanoid production, potentially modulating inflammation [54, 55]. Telmisartan's antioxidant and anti-inflammatory effects involve preventing nuclear factor-κB (NF-κB) signaling pathway activation [56].

Telmisartan exhibits pleiotropic effects, including anti-inflammatory, antioxidative, and antiproliferative actions in atherosclerosis and myocardial infarction.

It also demonstrates a protective effect against gastric mucosal lesions induced by stress and indomethacin [56, 57].

Telmisartan functions as a partial agonist at PPAR-γ, inducing catalase gene expression and inhibiting NF-κB. These actions collectively combat oxidative stress and downregulated a majority of pro-inflammatory responses [51, 58].

The anti-inflammatory impact of telmisartan is attributed to its PPAR-γ agonist activity. The modulation of PPAR-γ expression observed during various inflammatory disorders provides a robust foundation for utilizing potent PPAR-γ ligands, like telmisartan, to attenuate or modulate the progression of inflammation. This finding underscores the potential of PPAR-γ as a therapeutic target in inflammatory conditions, given its altered expression in several inflammatory disorders [59].

This sequence outlines the key mechanisms of action of telmisartan, emphasizing its dual role as an AT1 receptor antagonist and a partial agonist at PPAR-γ, contributing to its multifaceted effects on inflammation, oxidative stress, and related pathways.

Ulcerative colitis and telmisartan

There is a global rise in inflammatory bowel diseases (IBDs), particularly UC. Anti-TNF antibodies are commonly used for UC treatment. Telmisartan is a promising therapeutic candidate with anti-inflammatory properties. Telmisartan suppresses TNF-α-induced activation of nuclear factor-kB (NF-κB) in vascular endothelial cells [60]. Varying doses of telmisartan lead to decreased tissue levels of TNF-α and increased anti-inflammatory activity. Telmisartan's benefits extend to modulating colonic inflammation, oxidative stress, and apoptosis in inflammatory bowel disease [61].

Telmisartan administration mitigates pathological changes induced by arachidonic acid (AA)-induced colitis model, including oxidative stress, alterations in colonic weight, ulceration, tissue necrosis, and inflammatory infiltrate [62].

Telmisartan treatment accelerates the shift from the acute to the chronic phase of inflammation in UC [63]. Effectively it reduces neutrophil infiltration, as indicated by diminished myeloperoxidase (MPO) levels [64]. Telmisartan suppresses the expression of TNF-α and intervenes in the AA-induced colitis model by reducing malondialdehyde (MDA) levels, showcasing its protective role against oxidative cellular injury. Telmisartan increases levels of interleukin-10 (IL-10), known for its anti-inflammatory properties [63].

Telmisartan offers diverse anti-inflammatory effects in treating ulcerative colitis. By inhibiting NF-κB activation triggered by TNF-α, it reduces tissue TNF-α levels and enhances overall anti-inflammatory activity. Telmisartan also combats oxidative stress and apoptosis, common in colonic inflammation, and shields against AA-induced colitis. It expedites the shift from acute to chronic inflammation, curtails neutrophil infiltration, and dampens TNF-α expression. Furthermore, it lowers malondialdehyde levels, indicating defense against oxidative cellular harm, and boosts IL-10 levels, reinforcing its anti-inflammatory prowess. These combined actions highlight telmisartan's promise as a therapeutic option for ulcerative colitis.

Crohn's disease and telmisartan

Crohn's disease (CD) patients are often underweight, and there's a significant increase in the ratio of intra-abdominal adipose tissue to total abdominal fat in these individuals [65]. Mesenteric fat serves as a crucial indicator of intestinal inflammation in CD [66].

MAT in CD patients exhibits notable inflammatory infiltrate and altered adipocyte morphology compared to healthy subjects [67]. MAT comprises various cell types, including adipocytes, preadipocytes, macrophages,

endothelial cells, fibroblasts, and leukocytes. Telmisartan administration has a positive impact on mesenteric adipocytes in a mouse model of spontaneous colitis, restoring morphological changes and increasing adipocyte diameter. Mesenteric adipocytes contribute to C-reactive protein production in CD [68]. Leptin and adiponectin, hormones produced by adipose tissue, play roles in IBD pathogenesis [69].

Telmisartan treatment significantly alters the production of leptin and adiponectin in MAT, potentially influencing inflammatory processes. The neurotensin/miR-155 signaling pathway, involved in adipose inflammation and adipocyte differentiation, is modulated by telmisartan [70, 71].

Telmisartan treatment inhibits this pathway in MAT, suggesting a potential therapeutic contribution to attenuate MAT alteration and gut inflammation in CD. The renin-angiotensin system plays a role in the pathophysiology of colitis. Angiotensin receptor antagonists, including telmisartan, demonstrate effectiveness in preventing experimental colitis. Telmisartan exhibits a multifaceted impact on visceral adipose tissues, reducing leptin expression, increasing adiponectin levels, and attenuating MAT inflammatory parameters [72]. Telmisartan administration has a beneficial effect in an animal model of spontaneous colitis, reducing MAT inflammation, cytokine production, and ameliorating mesenteric adipose tissue alterations[73].

In conclusion, Telmisartan shows promise as a therapeutic option for managing inflammatory bowel diseases, particularly Crohn's disease, by influencing various aspects of adipose tissue composition, hormone regulation, and inflammatory pathways. The diverse actions of Telmisartan suggest its potential as a comprehensive approach to address the complex mechanisms associated with CD (Table 1 and Fig. 1).

Telmisartan in CNS disorders

Depression, characterized by anhedonia and persistent sadness, poses significant threats to life and cognitive functions [74, 75]. Stress plays a crucial role in depression development and associated memory issues. Ethical concerns limit direct research on depression causes and treatments in affected individuals. Chronic stress contributes to oxidative stress, leading to the generation of reactive oxygen species and compromised central nervous system functioning [76].

Chronic unpredictable mild stress (CUMS) rat model, introduced by Willner, simulates daily stressors and is instrumental in exploring depression origins and testing antidepressant interventions [77]. Telmisartan, a commonly used angiotensin receptor blocker (ARB), easily crosses the blood–brain barrier, inducing central AT1 receptor blockade [78].

Telmisartan holds promise as a potential oral antidepressant, possessing neuroprotective properties and mitigating cognitive impairments induced by chronic stress in rats [79].

Chronic stress results in decreased locomotor activity, sucrose preference, and impaired novel object recognition [80]. Telmisartan, especially at 1 mg/kg/day, significantly improves the impaired ability of novel object recognition, suggesting a potential antidepressant effect. AT1 receptor blockers, including telmisartan, gain attention for potential antidepressant effects [81].

The renin-angiotensin system (RAS) plays a crucial role in the body's response to stress [82].

Resting-state functional magnetic resonance imaging (r-fMRI), measuring intrinsic neural activity, is valuable in neuropsychiatric disorder research [83]. Telmisartan's impact on depression explored using ALFF and ReHo methods in a rat model was the first study of its kind. Telmisartan's effects on stress-induced alterations in brain regions were explored using ALFF and ReHo methods. Telmisartan at 1 mg/kg showed potential in reversing or attenuating stress-induced alterations in brain regions. Telmisartan demonstrated potential in decreasing hypercoordination of neural activity, particularly in the thalamus. Increased ReHo in limbic system regions and altered connectivity in various cerebral regions suggested neuroimaging markers for depression [81].

Telmisartan alleviated depressive behaviors induced by unpredictable chronic mild stress in BALB/c mice. Telmisartan's antidepressant effects were linked to its impact on serotonin transporter expression through PPARδ activation [84, 85].

Telmisartan's neuroprotective and antidepressant properties were associated with its impact on oxidative stress and pro-inflammatory mediators [86].

Its partial PPARδ agonistic property was considered crucial for reducing cytokine levels and improving cognitive decline [87].

Depression is a significant contributor to morbidity and mortality, requiring a multifaceted approach for accurate diagnosis and treatment [88, 89].

Telmisartan's dual action as an AT1 receptor blocker and PPAR-gamma agonist provides neuroprotection against various brain disorders, including depression [17, 90].

Telmisartan shows promise as a depression treatment through multiple mechanisms. It protects neurons, enhances cognition, and influences the body's stress response by modulating the renin-angiotensin system. Telmisartan also restores neural activity in stressed brain regions, impacting serotonin transporter expression via

Table 1 Role of telmisartan in inflammation

Type of study	Route of administration	Treatment duration	Target	Effect	References
a) Colitis					
3 mg/kg/day IL-10$^{-/-}$ mice	Oral	12 weeks	IFN-g and TNF-a, IL-6 and IL-17, leptin Adipoleptin	Increased adiponectin decrease in levels of leptin, IL-6, and IL-17	Li et al. [196]
b) Ulcerative colitis					
5 mg/kg (Wistar rats)	Oral	3 day before and 2h & 24 h after induction of disease	TNF-alpha, MPO, and MDA IL-10	Increase level of TNF-alpha, MPO, and MDA IL-10	Guerra et al. [2]
c) Neuronal Inflammation					
10 µmol/l (SK-N-SH human neuroblasts and primary rat cortical neurons)	Incubation of cells	Cells were incubated for 3 h	NADPH oxidase-4 (NOX-4) mRNA expression, NADPH oxidase activity, ROS generation, hydrogen peroxide-induced COX-2 gene expression, c-Jun N-terminal kinase (JNK), and c-Jun activation	Decreases in the IL-1β, mRNA expression, NADPH, hydrogen peroxide-induced COX-2 expression,	Pang et al. [27, 28]
d) Vasculitis					
5 mg/kg (Nephrectomized rats (Nx))	Intraperitoneal		PPAR-γ, NADPH, VCAM-1, Osteopontin,	Increase PPAR-γ, decrease NADPH oxidase, osteopontin, VCAM-1	Toba et al. [113]
e) Skin inflammation (psoriasis)					
40 mg/kg (K14-IL-17A ind/ + and IL-17A ind/ + mice)	Oral	4 weeks	IL-17A, AT II, PASI,	Increase in IL-17A, erythema, scaling, skin thickness, the affected area, and cumulative psoriasis area and severity index (PASI), decrease systolic blood pressure	Wild *et* al. [197]
f) Neuroinflammation					
100 µg/ml (Mouse Neuro2A neural cells)	Incubation of cells	Cells incubated for 24 h	PPAR-γ β-Actin, NF-κB, MyD88, cytokines IL-10	NF-κB, MyD88 activation, cytokines, motor co-ordination, cognitive functions, and activated SARM and PPAR-γ protein levels β-Actin, Increase secretion of IL-10	Balaji et al. [198]
g) Vascular Inflammation					
5 mg/kg (Male C57BL/6 mice)	Oral	13 weeks	GSK3b Ser^{9} phosphorylation, NF-kB p65	Inhibited hyperglycemia-induced NF-kB p65, inhibit GSK3b activity	Song et al. [1],

Table 1 (continued)

Type of study	Route of administration	Treatment duration	Target	Effect	References
h) Acute colitis					
0.01 and 5 mg/kg (Female C57Bl/6 J mice)	Rectal route	6 days	Tumor necrosis factor (TNF)-a, transforming growth factor (TGF)-b1, interleukin-1b and monocyte chemoattractant protein (MCP)-1, caspase-3 and -7	Increase anti-apoptotic protein Bcl-2, Decrease in mRNA levels of pro-inflammatory cytokines such as tumor necrosis factor a, interleukin-1b, interleukin-6 and monocyte chemoattractant protein 1 as well as cellular DNA damage, caspase-3 and -7	Arumugam et al. [199]
i) Chronic inflammation					
(0.1, 0.2. 0.4, 0.6, 1.5, 3 mg/kg) (Wistar rats)	Oral	6 days	Nuclear factor-jB signaling pathway, PPAR-c	Decreases paw edema, reactive oxygen species and pro-inflammatory mediators, PPAR-c	Walid et al. [200]
j) Endothelial Inflammation					
Human umbilical vein endothelial cell (HUVEC)s	Incubation of cells	48 h	Vascular (VCAM-1) and intercellular (ICAM-1)	Decrease in TNF-α-stimulated VCAM-1	Cianchetti et al. [207]
k) Retinal inflammation					
20 mg/kg (C57BL/6 mice)	Intraperitoneal	2 days	AT1R and AT2R	Increase in angiotensin II expression, decrease in synaptophysin and rhodopsin expression	Kurihara et al. [208]

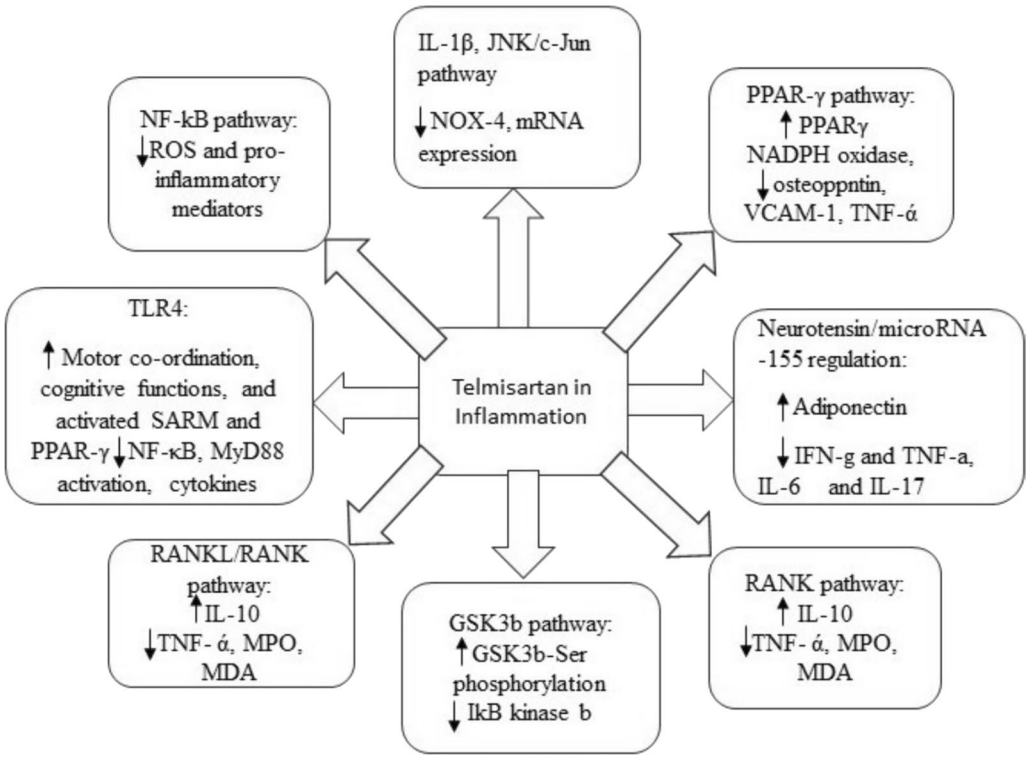

Fig. 1 Target effectors of telmisartan in inflammation. VCAM-1: Vascular cell adhesion molecule-1, RANK: receptor activator of nuclear factor-kappa B, MPO: myeloperoxidase, TNF-ά: tumor necrosis factor alpha, MDA: malondialdehyde, TLR4: toll-like receptors, IkB: inhibitor nuclear factor-kappa B

PPARδ activation. Its anti-inflammatory and antioxidant properties, partially through PPARδ agonism, alleviate depressive symptoms. Acting as both an AT1 receptor blocker and PPAR-gamma agonist, telmisartan offers comprehensive neuroprotection against depression.

Telmisartan in epilepsy

Epilepsies involve sudden, abnormal, and excessive neuronal activity in the brain, affecting 5–10% of the population. Long-term therapy challenges and medication side effects contribute to issues with compliance. Epilepsy may be associated with comorbid conditions like hypertension, diabetes, and renal disorders. Research suggests that drugs addressing these disorders, including ACE inhibitors and AT II receptor antagonists, may have a role in preventing seizures. The brain's RAS influences various functions, including regulating cerebral blood flow, stress, depression, seizures, and memory consolidation. Angiotensin II, a RAS component, acts as a neurotransmitter in the central nervous system, influencing the release of other neurotransmitters [91]. Angiotensin II inhibits GABAergic synaptic transmission by activating presynaptic AT1 receptors. Drugs like ACE inhibitors and AT1 receptor antagonists, including telmisartan, have the potential to enhance GABAergic transmission, beneficial in preventing seizures. Telmisartan, an AT1 receptor antagonist, improves the anticonvulsant effects of medications like valproate, lamotrigine, and topiramate in mouse models.

Telmisartan's unique properties, including potential depression-like effects, contribute to its anticonvulsant properties. Telmisartan exhibits neuroprotective effects by reducing local angiotensin II expression, blocking AT1 receptors, and promoting the relative upregulation of AT2 receptor function. In a rat model, ACE and AT1 receptors were upregulated in the brain after repetitive seizures. Telmisartan, especially at a 10 mg/kg dose, significantly decreases hind limb extension duration in the maximal electroshock (MES) model. Telmisartan exhibits substantial seizure inhibition and protection in the pentylenetetrazol (PTZ) test, suggesting dose-dependent antiepileptic activity. Telmisartan's slow dissociation from receptors, penetration of the blood–brain barrier, and increased potency at brain AT1 receptors contribute to its effectiveness. Telmisartan modulates the renin-angiotensin system, affecting glutamate/GABA release, decreasing glutamate levels, increasing GABA levels, and facilitating seizure prevention. AT1 receptor blockers, including telmisartan, contribute to decreased glutamate

levels, increased GABA levels, and potential seizure prevention [92].

Telmisartan's higher lipophilicity and potency at brain AT1 receptors make it effective in modulating these neurological functions [93]. Angiotensin affects ion channels, including voltage-dependent potassium and calcium currents, influencing neuronal excitability and seizures [94].

Stress-induced changes in cortical BZ1 receptor expression are regulated by AT1 receptor activity. AT1 receptor antagonists may protect against seizures induced by inflammatory cytokines in chronic inflammatory disorders [95]. Seizure generation involves the activation of inflammatory cytokines, and AT1 receptor antagonists can be considered for epilepsy treatment [96].

Telmisartan, with its AT1 receptor antagonistic properties, demonstrates promising antiepileptic effects. Understanding its mechanisms involving GABAnergic transmission, modulation of RAS, and impact on ion channels provides insights for potential therapeutic applications in epilepsy treatment. Together, these mechanisms underscore telmisartan's potential as an antiepileptic agent, providing neuroprotection, seizure management, modulation of neurotransmitter balance, and regulation of inflammatory pathways.

Telmisartan traumatic brain injury and cerebral edema

Cerebral edema is a serious complication of TBI, leading to elevated intracranial pressure and unfavorable clinical outcomes [97, 98].

The RAS is implicated in neuroinflammation and neurodegenerative disorders [99, 100].

Angiotensin receptor blockers (ARBs), especially telmisartan, effectively inhibit angiotensin II, offering anti-inflammatory and neuroprotective effects [101, 102]. Telmisartan, with its high lipid solubility, effectively penetrates brain tissue. Recognized for neuroprotective effects through angiotensin II receptor type-1 (AT1R) blockade [103].

Scientists investigated the anti-edemic effect of telmisartan through single oral gavage administration. Reduction in cerebral edema observed at 12 and 24 h post-TBI. The anti-edemic effect of telmisartan was not strictly dose-dependent [104]. Telmisartan demonstrated sustained inhibitory effects on AT1R, presenting an extended window for pharmacological intervention. IL-1β, a pro-inflammatory cytokine elevated in TBI, is implicated in cerebral edema [105, 106].

Telmisartan has shown efficacy in mitigating IL-1β-induced inflammatory responses in various brain injury models. Telmisartan improved neurological function, reduced lesion volume, and exhibited neuroprotective effects in the TBI model. Investigation into telmisartan's impact on the pro-inflammatory cytokine IL-1β. Telmisartan was found to inhibit the assembly and activation of the NLRP3 inflammasome [105, 107]. This inhibition provides a mechanism for telmisartan's anti-edemic role in TBI. The study confirmed the role of NLRP3 inflammasome-regulated IL-1β in traumatic cerebral edema. Telmisartan demonstrated potential in sustaining BBB integrity, reducing edema, and improving neurological function through NLRP3 inflammasome modulation [108].

Telmisartan, an angiotensin receptor blocker, offers a versatile approach to managing brain injury and cerebral edema. By inhibiting angiotensin II activity, it provides anti-inflammatory and neuroprotective benefits. Its lipid solubility enables direct brain tissue access for targeted action, primarily inhibiting AT1R to reduce inflammation and enhance neurological function. Telmisartan also disrupts NLRP3 inflammasome activation, reducing IL-1β-induced inflammation. Its sustained AT1R inhibition diminishes cerebral edema post-TBI, while also maintaining blood–brain barrier integrity. Telmisartan shows promise as a therapeutic agent for brain injury and cerebral edema management.

Anxiolytic effect of telmisartan

Anxiety disorders, affecting 7–30% of the world's population, represent a significant mental health challenge, contributing to economic burdens and health concerns [109]. Neurotransmitters like serotonin and GABA are implicated in anxiety pathophysiology, with selective serotonin reuptake inhibitors (SSRIs) recommended as first-line drugs. Emerging evidence suggests the involvement of the brain renin-angiotensin system in anxiety states, where angiotensin modulates neurotransmitter release [110]. Angiotensin receptor blockers (ARBs), used for cardiovascular conditions, have been associated with increased anxiety prevalence, particularly due to the blockade of AT1 > AT2 receptors in the brain [111]. Telmisartan, crossing the blood–brain barrier, exhibits significant anti-anxiety effects, possibly through AT1 receptor blockade in circumventricular organs and potential cerebral AT receptor blockade. The mechanism of telmisartan's anti-anxiety effects involves hypothesized upregulation of angiotensin levels and receptors in the brain during anxiety, influencing neurotransmitters like noradrenaline and serotonin [112]. Telmisartan's additional activities via PPAR-gamma and NADPH oxidase may contribute to its role in oxidative stress management, providing added benefits. [113].

In summary, telmisartan, through its action on the RAS and neurotransmitter modulation, emerges as a promising agent in managing anxiety, offering potential avenues for novel treatments targeting neurogenesis, plasticity, and cell survival (Table 2).

Table 2 Role of telmisartan in CNS disorders

Type of study	Route of administration	Treatment duration	Target	Effect	References
a) Stress-induced depression					
1 mg/kg (male Sprague–Dawley rats)	Oral	5 weeks	ReHo in the motor cortex, pons, thalamus, visual cortex, midbrain, cerebellum, hippocampus, hypothalamus, and olfactory cortex, B-A/B + A in the ORT	Decreased ReHo in the motor cortex and pons, increased ReHo in the thalamus, visual cortex, midbrain, cerebellum, hippocampus, hypothalamus, and olfactory cortex, Improved B-A/B + A in the ORT	Li et al. [81]
1 mg/kg (male BALB/c mice), (Rat-derived hippocampus H19-7)	Oral	6–7 weeks	PPAR-δ and 5-HTT	Reduced level of PPARδ and 5-HTT in hippocampus, Increased level of PPARδ and 5-HTT in H19-7 cell lines	Li et al. [89]
2 mg/kg (male albino mice)	Oral	2 weeks (15 days)	PPAR-gamma	Increased in PPAR-gamma, decrease in the immobility time	Brattiya and Sivaraman [90]
b) Epilepsy					
5 mg/kg, 10 mg/kg (Swiss albino mice)	Oral	1 h after test and standard drug administration	AT1, AT2	Blockade of AT1 receptors, increase in activity of AT2 receptors, Decease in hindlimb extensor phase, tonic hind limb extension	Pushpa et al. [92]
c) Cerebral edema					
5, 10, and 20 mg/kg (male C57BL/6 mice)	Oral	72 h	NLRP3, IL-1b, IL-18,	Decrease in NLRP3, IL-1b, IL-18, mRNA, and protein levels	Wei et al. [104]
d) Anxiety					
5 and 10mg/kg (Swiss albino mice	Oral	2 weeks	AT1	Stimulation of AT1, increase time spent in social interaction test, increase time spent in open arms	Swetha et al. [201]

Telmisartan in *cancer*

Endometrial *cancer*

Endometrial cancers are prevalent malignant tumors affecting the female genital tract, with a rising incidence [114, 115]. Despite the increasing incidence, effective agents for advanced and recurrent cases are lacking [115].

Peroxisome proliferator-activated receptor gamma and its ligands are known to induce apoptosis in various cancer types, including endometrial cancer [116, 117].

PPAR-gamma belongs to a nuclear hormone receptor family linked to endometrial carcinoma risk factors like obesity, excess estrogen, type II diabetes, and hypertension [118, 119].

Telmisartan emerges as a therapeutic option, inducing DNA damage and apoptosis in endometrial cancer cells. Telmisartan, acting as a partial agonist of PPAR-gamma, activates the receptor independently through AT1R interaction [51].

Telmisartan induces DNA double-strand breaks (DSBs) before triggering apoptosis in endometrial cancer cells. Among ARBs, only telmisartan inhibits cell viability in endometrial cancer, and this effect is diminished by a PPAR-gamma inhibitor (GW9662) [120].

PPAR-gamma immunoreactivity is detected in endometrial carcinoma tissue, and PPAR-gamma ligands show antiproliferative activity [116].

In vivo experiments using a nude mouse model demonstrate apoptosis within the tumor area in mice treated with telmisartan. Telmisartan's antitumor activity without major side effects suggests potential effectiveness in individuals with minimal residual disease post-surgery, chemotherapy, or radiotherapy [120].

In summary, telmisartan exhibits promise in endometrial cancer treatment through its involvement in PPAR-gamma mediated pathways, highlighting its potential as a therapeutic agent for individuals with minimal residual disease.

Telmisartan in colon *cancer*

Telmisartan, an angiotensin II receptor blocker (ARB) for hypertension, has been found to activate PPARγ in colon cancer cells, suppressing malignancy through differentiation and apoptosis [121].

Telmisartan effectively reduces cell viability, inhibits proliferation, and induces apoptosis in selected colon cancer cell lines [15].

The addition of GW9662, a PPARγ blocker, did not hinder telmisartan's inhibition of cell proliferation and viability, suggesting a PPARγ-independent pathway. Combined use of telmisartan and GW9662 intensified the reduction in cell viability and antiproliferative effects, particularly in SW-480 and SW-620 cells. Telmisartan demonstrated an apoptotic effect similar to pioglitazone, and this effect was not hindered by GW9662, indicating PPARγ-independent apoptosis induction [122]. Ligand-dependent activation of PPARγ resulted in the downregulation of PPARγ mRNA and upregulation of target genes, including CSTA. Telmisartan, in a dose-dependent manner, affected relative PPARγ mRNA expression and upregulated CSTA [123].

Addition of GW9662 led to significant downregulation in relative PPARγ mRNA expression, suggesting a PPARγ-independent pathway. Telmisartan's effects were superior to pioglitazone in certain cells, especially in the presence of the PPARγ blocker GW9662 [122].

Telmisartan's apoptotic effect was comparable to the full PPARγ agonist pioglitazone, and this action appeared to be independent of PPARγ [124, 125].

Examination of gene expression shed light on the influence of GW9662 on PPARγ and CSTA mRNA expression, providing valuable insights into the molecular mechanisms underlying telmisartan's effects on colon cancer cells [123].

In summary, telmisartan exhibits notable effects on colon cancer cells through a PPARγ-independent pathway, with enhanced efficacy in combination with GW9662. The study provides crucial molecular insights into telmisartan's actions on colon cancer cells, emphasizing its potential as a therapeutic agent.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the primary liver malignancy and a significant cause of cancer-related deaths globally [126, 127]. Telmisartan's impact on proliferation was assessed in various HCC cells, including HLF, HLE, HepG2, HuH-7, and PLC/PRF/5. Telmisartan effectively inhibited the proliferation of poorly differentiated HCC cells (HLF, HLE, and HepG2) while showing reduced sensitivity in well-differentiated HCC cells (HuH-7 and PLC/PRF/5) [128].

Telmisartan induced G0/G1 cell cycle arrest in HLF cells by impeding the G0-to-G1 transition [129].

The observed cell cycle arrest was accompanied by a significant reduction in the levels of cyclin D1, cyclin E, and other cell cycle-related proteins [130].

Telmisartan increased the activity of the AMP-activated protein kinase (AMPK) pathway and concurrently inhibited the mammalian target of rapamycin (mTOR) pathway [131, 132].

Telmisartan contributed to apoptosis in HLF cells, as indicated by an increase in caspase-cleaved cytokeratin 18 (cCK18) levels and a reduction in the phosphorylation of ErbB3. The study identified 163 differentially expressed miRNAs in response to telmisartan, emphasizing its inhibitory effects, particularly in poorly differentiated HCC cells. Telmisartan's mechanisms involve cell cycle regulation, apoptosis induction, and modulation of key signaling pathways like AMPK/mTOR [14].

Telmisartan exhibits potent antiproliferative effects against hepatocellular carcinoma (HCC), especially in poorly differentiated cells. It arrests the cell cycle at G0/G1 phase, reduces cyclin D1 and cyclin E expression, and activates the AMPK pathway while inhibiting mTOR, hampering HCC proliferation. Telmisartan also induces apoptosis by increasing cCK18 levels and decreasing ErbB3 phosphorylation in HLF cells. Altered miRNA expression underscores its efficacy, particularly in poorly differentiated HCC. Overall, telmisartan regulates the cell cycle, induces apoptosis, and modulates key signaling pathways like AMPK/mTOR, making it a promising therapy for HCC.

Ovarian *cancer* and telmisartan

Ovarian cancer, ranking third in incidence among female reproductive system malignancies, poses a significant health challenge with epithelial ovarian cancer having the highest mortality rate among gynecological tumors [133]. Challenges at advanced stages highlight the critical need for early detection strategies [134].

Peroxisome proliferator-activated receptor gamma (PPARγ), a key player in various cancers, emerges as a potential avenue for cancer intervention [135].

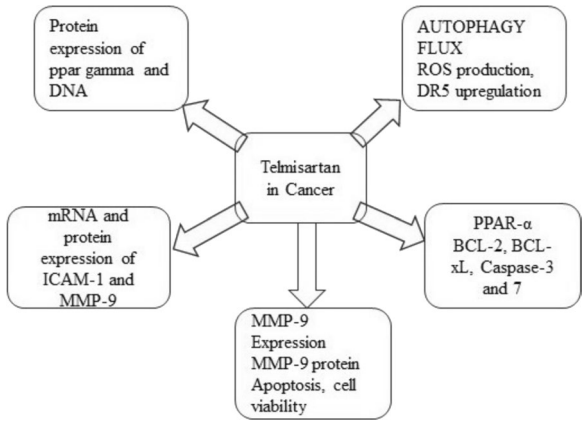

Fig. 2 Telmisartan in cancer. ICAM-1: intercellular adhesion molecule-1, MMP-9: matrix metalloprotease 9, ROS: reactive oxygen species, DR5: death receptor 5

Telmisartan, primarily an antihypertensive agent, gains attention for activating PPARγ. In HEY cells, telmisartan inhibits growth in a time- and dose-dependent manner, inducing apoptosis and reducing caspase-3 activity, consistent with outcomes in other cancer cells [136].

PPARγ's role takes center stage in regulating physiological processes, including ovarian tissue functions crucial for reproduction [137, 138]. Telmisartan's ability to elevate PPARγ expression reinforces its potential as a multifaceted therapeutic. Telmisartan's impact on MMP-9 expression, linked to cancer progression, further supports its potential in ovarian cancer treatment [139].

PPARγ agonists, including telmisartan, exhibit positive effects in contexts like renal fibrosis and early pregnancy chorionic villi, influencing trophoblast cell invasion [140]. Telmisartan's reduction in MMP-9 expression in HEY cells aligns with potential therapeutic effects observed in periodontitis and acute myocardial infarction [141, 142].

Telmisartan's mechanism of action in ovarian cancer encompasses PPARγ activation, suppressing cancer cell growth, promoting apoptosis, regulating MMP-9 expression, and offering potential multifaceted therapeutic effects (Fig. 2 and Table 3).

Telmisartan in diabetes

Telmisartan, recognized as an angiotensin II receptor antagonist specifically targeting the angiotensin II type-1 receptor, has become a widely utilized medication for the management of hypertension. In recent times, the focus on telmisartan's impact on peroxisome proliferator-activated receptors (PPARs) has expanded [10]. PPARs, belonging to the nuclear hormone receptor superfamily, are ligand-activated transcription factors. Telmisartan's distinctive feature lies in its reported partial PPARγ-agonistic effect, avoiding safety concerns associated with full PPARγ agonists [10].

Renowned for its partial PPARγ-agonistic effect, telmisartan exhibits capabilities in the regulation of glucose and lipid metabolism, improvement of insulin resistance, and potential effectiveness in addressing metabolic syndrome [10, 143].

Telmisartan's ability to lower glucose levels is linked to its capacity to inhibit reactive oxygen species and its agonistic influence on PPARγ [10]. The medication has demonstrated a reduction in oxidative stress, elevation of antioxidant levels, and enhancement of insulin sensitivity in individuals with diabetes [144]. The dual impact of telmisartan, involving partial activation of PPARγ and angiotensin type-1 receptor blockade, holds significance in preventing and managing type 2 diabetes mellitus (T2DM), metabolic syndrome, and atherosclerotic cardiovascular disease [10]. In hypertensive patients with T2DM, telmisartan exhibits favorable effects on insulin sensitivity, blood pressure, glucose and lipid metabolism, and endothelial function. Its cardioprotective attributes encompass the reduction of cardiac fibrosis and hypertrophy, prevention of adverse cardiac remodeling, and potential mitigation of diabetic cardiomyopathy [145]. Telmisartan's dual action on angiotensin type-1 receptor and PPARγ positions it as a valuable therapeutic option for hyperlipidemia, insulin resistance, hypertension, and stroke [146]. Additionally, the medication has displayed efficacy in improving the lipid profile, with notable reductions in triglycerides and increases in high-density lipoprotein cholesterol levels. Its potential hepatic partial PPARα agonist activity further contributes to its anti-dyslipidemic effects [147].

Telmisartan emerges as a promising therapeutic agent for T2DM, offering a comprehensive approach by addressing glucose regulation, lipid metabolism, insulin resistance, and providing cardiovascular and renal protection [10].

Telmisartan, known for its action as an angiotensin II receptor antagonist, also exhibits partial agonistic effects on PPARγ, distinct from full agonists. This feature enables telmisartan to regulate glucose and lipid metabolism and improve insulin sensitivity, making it valuable in managing type 2 diabetes mellitus (T2DM) and metabolic syndrome. By inhibiting reactive oxygen species and enhancing antioxidant levels through PPARγ activation, telmisartan reduces oxidative stress and enhances insulin sensitivity in diabetic individuals. Its dual action on PPARγ and angiotensin type-1 receptors provides a multifaceted approach to managing T2DM and metabolic syndrome.

Table 3 Role of telmisartan in cancer

Type of study	Route of administration	Treatment duration	Target	Effect	References
a) Human endometrial cancer cells					
1–100 mM (HHUA human endometrial cancer cell line, immunodeficient mice)	Incubation of cells	Cells are incubated for 48 h	Annexin V + /PI2, HHUA cells, caspase-3 and -7, PPAR-c, Bcl-2, Bcl-x	Increase annexin V + /PI2 fraction (early apoptotic) and annexin V + / PI + (late apoptotic) subpopulations, cleaved PARP in HHUA cells, caspase-3 and -7 Decrease in expression of Bcl-2 and Bcl-x	Koyama et al. [120]
b) Human colon cancer cells					
0.2–5 µM (Human colon cancer cells) (HT-29, SW-480, and SW-620)	Incubation of cells	Incubation of cells for 24 h with drug	PPARγ	Reduced cell survival in the HT-29, SW-480 and SW-620 cell, PPARγ mRNA expression, cell viability	Lee et al. [122]
c) Human Lung Adenocarcinoma					
10–100 µM (A549 cells)	Incubation of cells	Incubation of cells for 24–48 h with drug	PPARγ, mRNA, protetn,	Increase in mRNA and protetn expression of PPARγ, DNA binding activity of PPARγ, decrease in mRNA and protetn expression of ICAM-1 and MMP-9 survival rates and cell viabilities of A549 cells	Li et al. [196]
d) Colorectal cancer					
0.2mM (The human primary tumor (SW-480), metastatic (SW-620) colon cancer cell lines, and human immortal keratinocyte (HaCaT)	Incubation of cells	Incubation of cells for 24 h with drug	PPAR-gamma, HEY cells	Increase the expression of PPARγ, Inhibit growth of HEY cells	Puta et al. [202]
e) Lung cancer					
40 µM (A549, HCC-15)	Incubation of cells	Incubation of cells for 24 h with drug	ROS, DR5	Increase ROS production, Increase DR5 upregulation	Rasheduzzaman et al. [203]
f) Ovarian cancer					
10 and 100 µM (HEY human ovarian cancer cell)	Incubation of cells	Incubation of cells for 48 and 72 h with drug	PPARγ, MMP-9 protein	upregulating PPARγ, Increase Apoptosis, cell viability Decrease in MMP-9 protein expression,	Pu et al. [204]

Diabetic nephropathy

The renin-angiotensin system, vital for cardiovascular and renal functions, involves Angiotensin II (Ang II) binding to AT1 and AT2 receptors. Ang II, through AT1 receptor activation, induces vasoconstriction, sodium reabsorption, and various cellular processes in the kidney. Reactive oxygen species (ROS) [148] play a role in Ang II signaling, influencing critical events like transactivation of the epidermal growth factor receptor [149, 150].

In diabetic nephropathy (DN), PKC-α activation varies across renal structures, with implications for Na+-K+-ATPase inhibition and albumin uptake [151, 152]. Increased PKC-α expression correlates with TGF-β1 and VEGF levels, contributing to DN pathogenesis [153]. Telmisartan, an AT1R blocker, attenuates PKC-α and VEGF expression, suggesting nephroprotective effects via PKC-α in the RAS-PKC signaling cascade [154].

In vitro, telmisartan suppresses ROS generation induced by high glucose levels, protecting against cellular damage [155]. In diabetic mice, telmisartan reduces albuminuria, mesangial expansion, and inflammation-associated markers, demonstrating protective effects [156]. Telmisartan decreases oxidative stress markers (8-OHdG, Nox4), apoptosis (Bax), and improves kidney function and structure in diabetic rats. It regulates mitochondria-related pathways, inhibiting oxidative stress [157, 158].

Telmisartan's dual action as a PPAR-gamma agonist and AT1 receptor inhibitor contributes to renal protection It downregulates gene expression in the oxidative phosphorylation pathway, potentially inhibiting excessive mitochondrial ROS production [159, 160]. The upregulation of nephrin and podocin, crucial components of the slit diaphragm, signifies protective effects against diabetic nephropathy [161, 162].

Telmisartan exhibits multifaceted renoprotective effects, addressing oxidative stress, inflammation, and apoptosis in diabetic nephropathy. Its actions on PKC-α and various pathways provide valuable insights, suggesting its therapeutic potential in managing diabetic kidney disease (Fig. 3).

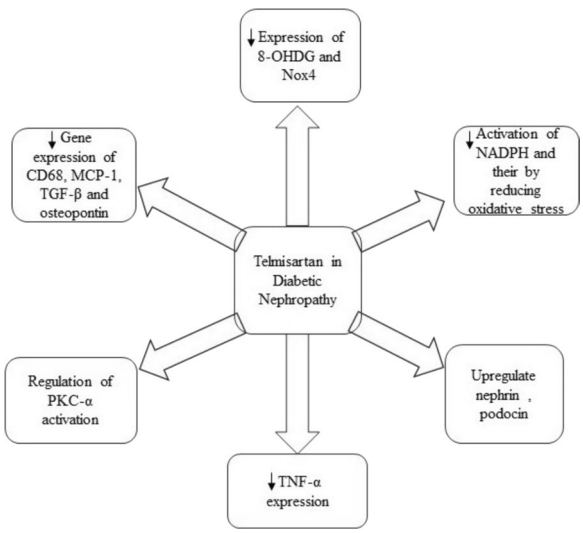

Fig. 3 Telmisartan in diabetic nephropathy. TGF-b: Transforming growth factor beta, 8-OHdG: 8-hydroxydeoxyguanosine, (MCP)-1: monocyte chemoattractant protein, CD68: cluster differentiation, TNF-α: tumor necrosis factor alpha, PKC-α: protein kinase C alpha, Nox4: NADPH oxidase-4, NADPH: nicotinamide adenine dinucleotide phosphate

Diabetic neuropathy

Nerve healing is influenced by various factors, including the time between trauma and surgery, severity of trauma, type of damaged nerve, patient's age, and surgeon's experience [163]. Peripheral nerve regeneration is closely tied to apoptosis, and inhibiting the renin-angiotensin system (RAS) receptors, especially AT1 receptors, reduces apoptosis, inflammation, and oxidative stress [102]. Telmisartan, with its high affinity for AT1 receptors, demonstrates anti-inflammatory effects, supporting positive effects on nerve healing [102, 164].

The PPAR-γ ligand in telmisartan mediates its positive effects by inhibiting post-ischemic inflammation, neuronal degeneration, and apoptosis regeneration [165]. Telmisartan attenuates hemorrhage expansion, perihematomal edema formation, and neuropathic pain, attributed to its anti-inflammatory properties [102, 166]. It prevents nerve cells from injury by decreasing the apoptotic pathway, inhibiting caspase-3 activity, and reducing inflammatory cytokines [167, 168]. In conditions like chronic constriction injury (CCI), RAAS overactivation is associated with increased inflammatory mediators, oxidative stress, and pain-related markers [169, 170]. Telmisartan, by modulating RAAS components and downregulating signaling pathways like JAK2/STAT3 and P38-MAPK, [171] exerts beneficial effects in neuropathic pain modulation. ACE-Is are superior to ARBs in neuroprotective and antioxidant effects [172].

Telmisartan administration in diabetic rats prevents the progression of diabetic neuropathy (DN) and enhances thermal and mechanical analgesia [12]. Its anti-inflammatory and neuroprotective properties, [27] attributed to PPAR-γ activation, alleviate hyperglycemia-associated alterations and reduce pro-inflammatory biomarkers [12]. Telmisartan suppresses the production of inflammatory cytokines and inhibits thermal hyperalgesia development and progression. It attenuates nerve growth factor degeneration and behavioral abnormalities in diabetic animals [173].

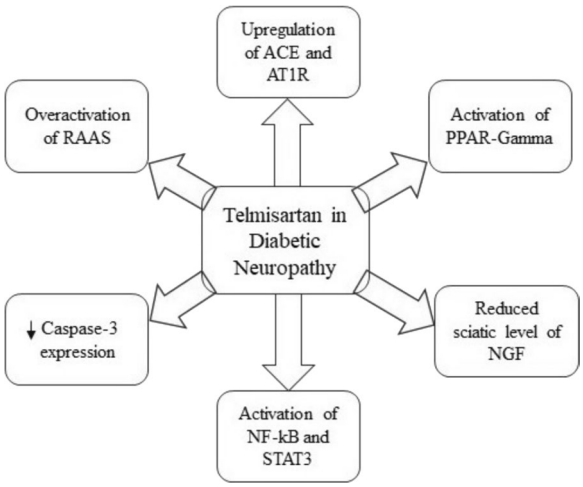

Fig. 4 Telmisartan in diabetic neuropathy. PPAR-G: peroxisome proliferator-activated receptor gamma, RAAS: renin–angiotensin–aldosterone system, STAT3: signal transducers and activators of transcription, NF-kB: nuclear factor-kappa B, NGF: transforming growth factor

In summary, telmisartan's multifaceted actions, involving anti-inflammatory, neuroprotective, and antioxidant effects, position it as a potential therapeutic candidate in nerve healing and diabetic neuropathy. Its modulation of RAAS components and downstream signaling pathways contributes to its beneficial effects on nerve regeneration and pain modulation (Fig. 4).

Diabetic retinopathy

The activation of the renin-angiotensin system, particularly through the angiotensin II type-1 receptor (AT1R), has been identified as a potential mechanism for damaging retinal neurons in individuals with diabetes [174]. TNFα, a key inflammatory factor, can disrupt the blood-retinal barrier (BRB), leading to leukocyte accumulation in the retina and promoting cell death [175]. Caspase, indicators of cell death, are activated early in the retina of individuals with diabetes. Telmisartan effectively reduces caspase-3 activity in the diabetic retina, providing protection against neuronal damage [174]. The AT1R blocker effect extends to modulating levels of brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), tyrosine hydroxylase (TH), glutathione (GSH), and caspase activity in the retina [174]. Telmisartan, by inhibiting AT1R activation, addresses imbalances in these factors contributing to neurodegeneration in diabetic retinopathy. Telmisartan's ability to inhibit AT1R, which is stimulated by angiotensin II, presents a promising approach for treating diabetic retinopathy (DR) [176]. Telmisartan demonstrates a multifaceted protective role in diabetic retinopathy (DR). By inhibiting the activation of the angiotensin II type-1 receptor (AT1R) [177], telmisartan intervenes in the renin-angiotensin system (RAS), a potential mechanism implicated in damaging retinal neurons in diabetes [178].

The drug effectively reduces caspase-3 activity, providing protection against early cell death in the diabetic retina. Telmisartan's impact extends to the modulation of various factors crucial for neurodegeneration in diabetic retinopathy. It addresses imbalances in brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), tyrosine hydroxylase (TH), and glutathione (GSH), offering a promising approach for treating DR [179]. Its high affinity for AT1 receptor subtypes allows telmisartan to effectively block the RAS, leading to a sustained protective effect and slowing down the progression of diabetic retinopathy [180, 181]. The neuroprotective effects of telmisartan are further highlighted by its ability to elevate BDNF and GSH levels in both blood and the retina, responding to oxidative stress. By blocking AT1R activation induced by diabetes [182], telmisartan may deactivate NADPH oxidase, reducing oxidative stress and potentially increasing BDNF levels. The preservation of neurons, indicated by increased levels of TH, reinforces the protective impact of Telmisartan, particularly on dopaminergic amacrine cell functionality [183]. In addition, telmisartan effectively suppresses the elevated expression of VEGF-A, RAGE, and TNF-α in the retina, contributing to the mitigation of retinal complications [184]. Its specific binding to intraocular angiotensin receptor 1 (ATR 1) inhibits excessive activation of the Ang II-mediated RAS system, postponing the breakdown of the blood-retinal barrier (BRB) [184]. Telmisartan's actions encompass inhibition of AT1R, modulation of neuroprotective factors, reduction of oxidative stress, and suppression of pro-inflammatory mediators [185].

Telmisartan exerts a multifaceted protective effect against retinal damage in diabetic retinopathy by inhibiting AT1R, modulating neuroprotective factors, reducing oxidative stress, suppressing pro-inflammatory mediators, and preserving the blood-retinal barrier (Fig. 5).

Telmisartan and diabetic ulceration

Patients diagnosed with type 2 diabetes mellitus frequently experience a high incidence of acute gastric inflammation and ulcer disease, and this occurrence is notably linked to the duration of diabetes. Moreover, peptic ulcers associated with diabetes mellitus tend to be more severe, exhibiting a delayed healing rate and a higher propensity for complications, including gastrointestinal bleeding [186, 187].

The heightened vulnerability of gastric mucosa in diabetic animals to damage involves a multifaceted mechanism. This

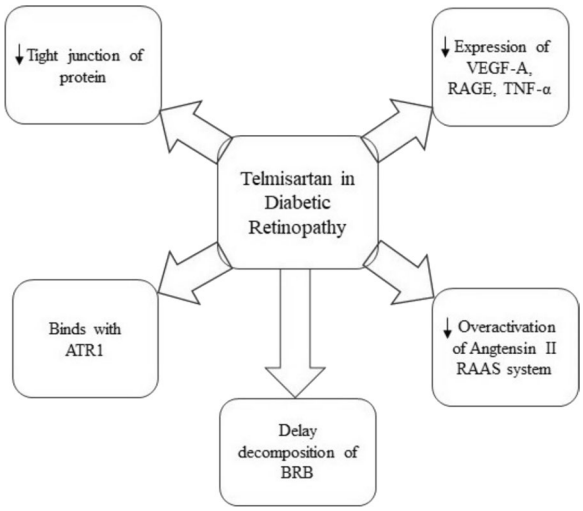

Fig. 5 Telmisartan in diabetic retinopathy. BRB: Blood retina barrier, VEGF: vascular endothelial growth factor, RAGE: receptor for advanced glycation end products, TNF-α: tumor necrosis factor alpha, RAAS: renin–angiotensin–aldosterone system

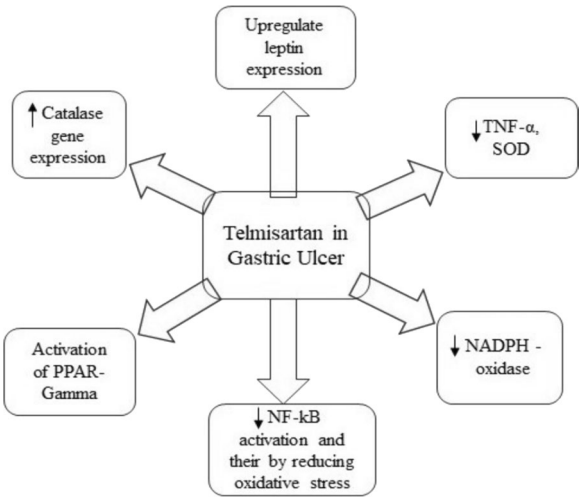

Fig. 6 Telmisartan in diabetic ulcer. SOD: Superoxide dismutases, NF-kB: Nuclear factor-kappa B, PPAR-G: peroxisome

includes changes in gastric motility [188] compromised duodenal bicarbonate secretion, and diminished angiogenesis, along with dysfunction in capsaicin-sensitive neurons crucial for safeguarding the gastric mucosa [189]. Telmisartan, a medication utilized for various conditions, exhibits antioxidant and anti-inflammatory properties attributed to its inhibition of the nuclear factor-κB (NF-κB) signaling pathway. This pathway plays a pivotal role in the transcription of genes involved in oxidative stress and inflammation, including NADPH oxidase, tumor necrosis factor-α (TNF-α), and inducible nitric oxide synthase (iNOS). Angiotensin II, a known inducer of oxidative stress, activates NADPH oxidase, leading to the production of reactive oxygen species (ROS) like superoxide anion, hydrogen peroxide, and hydroxyl radicals [190]. Moreover, it triggers inflammatory pathways, promoting the synthesis of TNF-α, contributing to gastric mucosa damage. Telmisartan acts as a partial agonist for the nuclear peroxisome proliferator-activated receptor-γ (PPAR-γ). Activation of PPAR-γ stimulates the expression of the catalase gene and inhibits NF-κB activity, thereby mitigating oxidative stress and reducing pro-inflammatory reactions [191, 192]. Stimulation of PPAR-γ also enhances the production of leptin protein, known for its ability to reduce gastric acid secretion [193]. The drug's impact on gastric health extends to blocking the activation of caspase-3 in the stomach lining, preventing the cascade of events leading to cell apoptosis [194]. Pro-inflammatory cytokines, especially TNF-α, and oxygen-derived free radicals are triggers of cell death by activating caspases. Telmisartan's ability to inhibit apoptosis is likely due to its capacity to reduce reactive oxygen species production and inhibit the synthesis of TNF-α and excessive nitric oxide [102, 195].

In summary, Telmisartan's mechanism of action involves inhibiting NF-κB signaling, reducing oxidative stress, suppressing inflammatory responses, and preventing apoptosis, collectively contributing to its potential therapeutic role in protecting against gastric ulcer formation (Fig. 6 and Table 4).

Conclusion

Telmisartan demonstrates neuroprotective effects by targeting inflammation and oxidative stress pathways, potentially useful in neurodegenerative diseases. It also exhibits significant anti-inflammatory properties, particularly in mitigating acute ocular inflammation associated with endotoxin-induced uveitis (EIU). It shows promise in mitigating diabetes-induced vascular inflammation by reducing adhesion molecule expression and inflammatory leukocyte attachment. It also exhibits nephroprotective benefits by modulating PKC-α and VEGF expression. Telmisartan, alleviate neuropathic pain by modulating RAAS components and suppressing JAK2/STAT3 and P38-MAPK signaling pathways. Telmisartan, acting as an AT1 receptor antagonist and PPAR-γ partial agonist, displays antioxidative and anti-inflammatory effects, impacting metabolic and inflammatory pathways. It suppresses TNF-α-induced NF-κB activation, reducing neutrophil infiltration in ulcerative colitis.

Additionally, its ACE inhibitor and AT1 receptor antagonist properties may augment GABAergic transmission, potentially benefiting seizure prevention and reducing edema in traumatic brain injury. Telmisartan

Table 4 Role of telmisartan in diabetes

a) Diabetic Nephropathy					
5mg/kg/day Telmi [Male db/db and db/m mice]	Intraperitoneal	9 weeks	CD68, MCP-1, TGF-β osteopontin 8-OHdG Nox4 Bax, ROS	Reducing oxidative stress, decreased expression of 8-OHdG and Nox4, increased expression levels of the macrophage marker CD68, the chemokine MCP-1	Sato-Horiguchi et al. [156]
9 mg/kg/day—Telmi, [100 mg/kg-STZ (i.p.), Male C57BL/6 mice]	Orally	6 weeks	PKC-α pathway, ARB	Increased expressions of TGF-β1 and VEGF, decreased activation of PKC-α	Yao et al. [205]
5 and 10 mg/kg—Telmi 60mg/kg-STZ (i.p.), [Male Sprague–Dawley rats]	Orally	12 weeks	Analyses of individual genes, pathway enrichment, GO terms annotation, oxidative phosphorylation pathway, PPAR-g pathway, slit diaphragm	Increased glucose, H2O2, decreased MDA, inhibit overproduction in superoxide and ROS, suppressed AT1R expression	Zhang et al. [162]
b) Diabetic Neuropathy					
10 mg/kg-Telmi, [Male Wistar rats] Traumatization of sciatic nerves	Orally	4 weeks	(IL-1β) gene expression, TNF-alpha and interferon-gamma (IFN-γ), caspase-3 mRNA expression, PPAR-γ pathway	Increase mRNA expression, decrease caspase-3,	Yuksel et al. [167]
5 mg/kg-Telmi [Male albino rats] CCI of the sciatic nerve	Orally	2 weeks	NFκB signaling pathway TNF-α, NADPH oxidase and catalase, STAT3 activation, P38-MAPK pathway ACE, AT1R, AT2R, ACE, ARBs	Increased GFAP expression, COX-2, PGE2 level, decreased MBP expression,	Hegazy et al. [7, 172]
5 and 10 mg/kg/day-Telmi, (55 mg/kg)-STZ (i.p.) [male Wistar albino rats]	Orally	4 weeks	Tumor necrosis factor-α, interleukin-1β, and interleukin-6, Nerve growth factor (NGF), COX-2, MMP-2, and MMP-9, PPAR-γ activation pathway	Increase in pro-inflammatory biomarkers, inhibited NGF levels, decrease in glucose levels, mean body weights	Al-Rejaie et al. [12]
c) Diabetic Retinopathy					
10 mg/kg/day-Telmi, 55 mg/kg-STZ (i.p.), [Male Wistar rats]	Orally	9–10 weeks	RAS receptors, AT1R blockers, NADPH oxidase	Increases the GSH level, improving the protein expression level of BDNF, CNTF, and TH, decreases the caspase-3	Ola et al. [174]
10mg-Telmi, 50mg/kg-STZ (i.p.), [C57BL/6J mice]	Intravitreal	6 months	ATR1, RAAS system, VEGF, RAGE, TNF-ά, NF-κB and PKC pathways	Increase endothelial vascular growth inducer, decrease in tight junction proteins	Cao et al. [184]
d) Diabetic ulceration					
1 mg/kg/day-Telmi, 60 mg/kg-STZ (i.p.), [Male Sprague–Dawley rats]	Orally	1 week	Tumor necrosis factor-α, nuclear factor-κB, Caspase-3 PPARγ pathway	Increased lipid peroxidation, decreased the vulnerability of the gastric mucosa	Fouad et al. [206]

shows anti-anxiety effects by blocking AT1 receptors in the brain and may inhibit cerebral AT receptors. It also demonstrates potential as a therapy for endometrial and colon cancer by inducing DNA damage and apoptosis through PPAR-gamma activation. Telmisartan inhibits the proliferation of poorly differentiated hepatocellular carcinoma cells and reduces MMP-9 expression in ovarian cancer cells.

Limitations

Our findings are limited by our main focus on preclinical studies, which means we did not review the effects of telmisartan in clinical studies. Moreover, our attention was directed toward assessing telmisartan's impact on common diseases and disorders, rather than those that are rare.

Abbreviations

ARB	Angiotensin receptor blocker
AT1	Angiotensin II type-1
CD	Crohn's disease
EIU	Endotoxin-induced uveitis
GSK3β	Glycogen synthase kinase-3 beta
IBDs	Inflammatory bowel diseases
ICAM-1	Intercellular adhesion molecule
IFN-g	Interferon gamma
TNF	Tumor necrosis factor
IKKβ	Inhibition if nuclear factor-kB (IkB) kinase beta
IL	Interleukin
JNK	Jun N-terminal kinase
LPS	Lipopolysaccharide
MAT	Medication-assisted treatment
MCP	Monocyte chemoattractant protein -1
MDA	Malondialdehyde
MPO	Myeloperoxidase levels
PASI	Psoriasis area and severity index
PPAR-γ	Peroxisome proliferator-activated receptor
RANKL/RANK	Signaling pathway
SARM	Selective androgen receptor modulator
TLRs	Toll-like receptors
VCAM-1	Vascular cell adhesion molecule-1
CUMS	Chronic unpredictable mild stress
r-fMRI	Resting-state functional magnetic resonance imaging maximal electroshock (MES) model
PTZ	Pentylenetetrazol test
SSRIs	Selective serotonin reuptake inhibitors
5-HTT	Serotonin
DSBs	DNA double-strand breaks
HCC	Hepatocellular carcinoma
AMP	Activated protein kinase (AMPK) pathway
(mTOR)	Mammalian target of rapamycin pathway
cCK18	Caspase-cleaved cytokeratin 18
MMP-9	Matrix metalloprotease 9,
ROS	Reactive oxygen species,
DR5	Death receptor 5
TGF-b	Transforming growth factor beta
8-OHdG	8-Hydroxydeoxyguanosine
MCP-1	Monocyte chemoattractant protein
CD68	Cluster differentiation
TNF-α	Tumor necrosis factor alpha
PKC-α	Protein kinase C alpha
CCI	Chronic constriction injury

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Availability of data and materials
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable for this work.

Consent for publication
The authors declare no conflict of interest.

Competing interests
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